Research

Pharmaceutical Engineering—Review

Cardiac Remote Conditioning and Clinical Relevance: All Together Now!

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ABSTRACT Acute myocardial infarction (AMI) is the leading cause of death and disability worldwide. Timely reperfusion is the standard of care and results in decreased infarct size, improving patient survival and prognosis. However, 25% of patients proceed to develop heart failure (HF) after myocardial infarction (MI) and 50% of these will die within five years. Since the size of the infarct is the major predictor of the outcome, including the development of HF, therapies to improve myocardial salvage have great potential. Over the past three decades, a number of stimuli have been discovered that activate endogenous cardioprotective pathways. In ischemic preconditioning (IPC) and ischemic postconditioning, ischemia within the heart initiates the protection. Brief reversible episodes of ischemia in vascular beds remote from the heart can also trigger cardioprotection when applied before, during, or immediately after myocardial ischemia—known as remote ischemic pre-, per-, and post-conditioning, respectively. Although the mechanism of remote ischemic preconditioning (RIPC) has not yet been fully elucidated, many mechanistic components are shared with IPC. The discovery of RIPC led to research into the use of remote non-ischemic stimuli including nerve stimulation (spinal and vagal), and electroacupuncture (EA). We discovered and, with others, have elucidated mechanistic aspects of a non-ischemic phenomenon we termed remote preconditioning of trauma (RPCT). RPCT operates via neural stimulation of skin sensory nerves and has similarities and differences to nerve stimulation and EA conducted at acupoints. We show herein that RPCT can be mimicked using electrical stimulation of the abdominal midline (EA-like treatment) and that this modality of activating cardioprotection is powerful as both a preconditioning and a postconditioning stimulus (when applied at reperfusion). Investigations of these cardioprotective phenomena have led to a more integrative understanding of mechanisms related to cardioprotection, and in the last five to ten years, it has become clear that the mechanisms are similar, whether induced by ischemic or non-ischemic stimuli. Taking together much of the data in the literature, we propose that all of these cardioprotective "conditioning" phenomena represent activation from different entry points of a cardiac conditioning network that converges upon specific mediators and effectors of myocardial cell survival, including NF-κB, Stat3/5, protein kinase C, bradykinin, and the mitoK$_{ATP}$ channel. Nervous system pathways may represent a novel mechanism for initiating conditioning of the heart and other organs. IPC and RIPC have proven difficult to translate clinically, as they have associated risks and cannot be used in some patients. Because of this, the use of neural and nociceptive stimuli is emerging as a potential non-ischemic and non-traumatic means to initiate cardiac conditioning. Clinical relevance is underscored by the demonstration of postconditioning with one of these modalities, supporting the conclusion that the development of pharmaceuticals and electroceuticals for this purpose is an area ripe for clinical development.

1 Introduction

In 1986, Murry et al. [1] first described ischemic preconditioning (IPC), in which brief episodes of ischemia/reperfusion (I/R) preceded an injurious I/R resulting in reduced myocardial infarct size in a canine model. The phenomenon of IPC has since been successfully demonstrated in multiple animal species including dogs, rats, pigs, rabbits, and mice, as well as confirmed in human patients [2–7]; reviewed in Ref. [8]. Marber et al. [9] reported a second window of protection (late preconditioning), which develops 12–24 h after the initial preconditioning stimulus. Unlike early IPC, which is power-

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ful but short-lived, late IPC remains protective for 24–72 h, although the magnitude of the protection is less over time [3]. Repeated preconditioning episodes of the same type are neither additive nor cumulative [10].

In 1993, Przyklenk et al. [11] demonstrated that in the canine heart, a preconditioning stimulus applied to the vascular bed supplied by the circumflex branch reduced infarct size in the area of the myocardium supplied by the left anterior descending coronary artery. Subsequently, it was demonstrated by McClanahan et al. [12] that cardioprotection could even be achieved by preconditioning ischemic stimuli in distant organ sites, such as the kidney. Remote ischemic preconditioning (RIPC) has been demonstrated to elicit cardioprotection following ischemia of kidneys, intestine, limbs, liver, skeletal muscle, and brain (reviewed in Ref. [13]). While the release of diffusible factors from ischemic preconditioned tissues/organs is a key aspect of RIPC [14–18], it is also evident that neural connections to the preconditioned limb or tissue are required. For instance, it has been shown in most [19] but not all [20] animal models that blocking sympathetic transmission using hexamethonium abrogates RIPC's protective effect. In a mouse hindlimb model, it has been demonstrated that either occlusion of the femoral vein or transection of the femoral and sciatic nerves likewise abolishes the cardioprotection observed after RIPC, indicating the requirement for both humoral and neural pathways [21]. RIPC has been shown to improve short- and long-term clinical outcomes when applied prior to emergency or elective percutaneous intervention [22], coronary artery bypass grafting [23], and valve replacement [24]. Many of the detailed mechanistic aspects of RIPC are shared with IPC (see below). Although IPC and RIPC have emerged as powerful methods of ameliorating I/R injury to the myocardium, their use as clinical cardioprotective strategies to attenuate the pathophysiological consequences of I/R injury (i.e., infarction and ventricular dysfunction) is limited by the inability to predict the onset of clinical ischemia.

As a direct result of considering this limitation, Zhao et al. [25] demonstrated that rapid sequential intermittent interruption of coronary blood flow during the early moments of reperfusion after ischemia attenuates I/R injury. This phenomenon, termed postconditioning, is extremely valuable in that it supports the efficacious use of repetitive ischemia at a clinically relevant time point (e.g., at reperfusion) [26]. The more recent findings in this field [27–30] have combined postconditioning and RIPC concepts by demonstrating that ischemia of a remote site (such as a limb) can elicit cardioprotection at reperfusion. A related phenomenon, perconditioning, results from administering a cardioprotective stimulus during the I/R injury [31, 32]. Remote perconditioning involves using a conditioning stimulus at a remote site during myocardial infarction (MI), and has been shown to be protective and to have clinical value [24]. However, all of these cardioprotective strategies have a limitation in that they require the use of an ischemic stimulus to an organ; this is often not clinically desirable. Furthermore, clinical trials of such approaches have been disappointing [33], and/or come with significant limitations and risks that prevent their use [34, 35]. The clinical trials of remote ischemic conditioning have some limitations,

mainly as a result of including too few subjects, and of confounding variables inherent within the patient population. The patients involved are of heterogeneous age and overall health; many have co-morbidities that are known to reduce the efficacy of cardioprotection, and are administered drugs that mask or block cardioprotection [8]. Furthermore, factors such as collateral circulation and spontaneous or very early clinical reperfusion can lead to small infarcts that do not benefit from adjunctive therapy [13].

Even though recent results with limb ischemia have supported cardioprotection in humans [36], this approach can be difficult to tolerate and cannot be employed in some patients, including the morbidly obese, or patients who have had axial lymphadenectomy. An alternative would be to achieve cardioprotection using a non- or minimally-invasive technique, such as a remote non-ischemic stimulus. Cardioprotection has been shown to result from non-ischemic stimuli including nerve stimulation (spinal, vagal, femoral), acupuncture and electroacupuncture, skin incision, and the chemical or electrical treatment of skin [37–43]. To the extent that some of these modalities are less traumatic yet efficacious, they are being studied as potential therapies.

2 IPC, RIPC, and cardiac conditioning

Over the past 25 years, we have learned a great deal about the detailed mechanisms that underlie cardioprotection in general, and IPC, RIPC, and related phenomena specifically. Mechanistic studies usually focus upon initiators, mediators, and effectors of protection, though over the years, our insights have blurred some of these distinctions.

Clearly, understanding the mechanism of cardioprotection after IPC, RIPC, and postconditioning has the potential to elucidate potential therapeutic targets that could be used to initiate or intensify cardioprotection. These targets could be useful in preconditioning in certain situations, including preventing/reducing perisurgical MI and treating patients at risk for MI [5, 44, 45]. Alternatively, understanding the mechanism may be the key to discovering more clinically applicable ways to initiate perconditioning and/or postconditioning in the clinical setting. Generally speaking, similar—yet not identical—mechanisms underlie the mediator and effector aspects of diverse protective stimuli including IPC, RIPC, preconditioning, postconditioning, and perconditioning [46]. The most diverse aspect of cardioprotective phenomena seems to be in the initiating phase, but this may simply represent the point of stimulation in a more general convergent mechanism. There are some distinct mechanistic differences and specific pathways that have been shown not to be necessary for certain types of cardioprotective stimuli. Combinatorial studies (use of multiple stimuli) have sometimes shown additive effects supporting mechanistic differences [47, 48]. However, other combinations have not shown such effects, supporting a similarity or at least an overlap of mechanism. In this paper, we compare and contrast some of these data, extract some meaning, and add to what is known in a way that may point to more efficacious and practical types of cardioprotection to invoke in a clinical setting.